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Attorneys for Defendants Apotex, Inc. and Apotex Corp.

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY**

ASTRAZENECA LP and	:	
ASTRAZENECA AB,	:	Civil Action No.: 1:09-CV-1518
	:	(RMB) (AMD) consolidated into Civil Action
Plaintiffs,	:	No.: 1:08-CV-1512
	:	
v.	:	
	:	
APOTEX, INC. and APOTEX CORP.,	:	
	:	
Defendants.	:	
	:	

**DECLARATION OF RICHARD N. DALBY, PH.D., IN SUPPORT OF
DEFENDANTS APOTEX, INC.'S AND APOTEX CORP.'S
RESPONSIVE CLAIM CONSTRUCTION BRIEF**

I, RICHARD N. DALBY, Ph.D., based on personal knowledge, hereby declare as follows:

1. I make this declaration in support of Defendants Apotex, Inc.'s and Apotex Corp.'s (collectively "Apotex") Responsive Claim Construction Brief Pursuant to the Court's March 15, 2010 Scheduling Order.

2. I am familiar with the facts stated herein and, if called to testify, would competently testify thereto.

3. I was retained by St. Onge Steward Johnston & Reens LLC, counsel for Apotex, as an expert in this case. I am being compensated at an hourly rate of \$700. My compensation is not contingent upon the outcome of this litigation.

4. I understand that Plaintiffs AstraZeneca LP and AstraZeneca AB (collectively "AstraZeneca") accuse Apotex of infringing the following patents: U.S. Patents No. 6,598,603 ("the '603 patent"), U.S. Patent No. 6,899,099 ("the '099 patent"), and U.S. Patent No. 7,524,834 ("the '834 patent").

5. The opinions set forth in this declaration are based on my personal knowledge and my review of the '603, '099 and '834 patents.

I. BRIEF STATEMENT OF BACKGROUND AND QUALIFICATIONS

6. A brief statement of my background and qualifications is set forth in my declaration in support of Apotex's Opening Claim Construction Brief, submitted on December 4, 2009. My educational background, work experience, and publications are also set forth in full in my *curriculum vitae*, attached to as Exhibit 1 thereto.

II. PERSON OF ORDINARY SKILL IN THE ART

7. My opinion of the qualifications and experience of one of ordinary skill in the relevant art is set forth in my declaration in support of Apotex's Opening Claim Construction Brief, submitted on December 4, 2009.

III. STATEMENT OF OPINION

8. I have read and reviewed the '603, '099 and '834 patents. It is my opinion that the following disputed terms in these patents would be understood by one of ordinary skill in the art as follows:

A. Disputed Claim Terms from the '603 and '099 Patents

Budesonide Composition

9. I have considered the term "budesonide composition" as used in claims 1, 3, 5, 8, 10, 11, 13, 15 and 17-29 of the '603 patent.

10. It is my opinion a person of ordinary skill in the art would understand that a "budesonide composition" refers to budesonide molecules combined with one or more substances, in the form of a solution or suspension.

11. This construction is consistent with relevant dictionary definitions, which define the term "composition" as "a product of mixing or combining various elements or ingredients." (Gross Decl. Ex. G, excerpt from WEBSTER'S NINTH NEW COLLEGIATE DICTIONARY (1991)).

12. Moreover, one of ordinary skill in the art would understand that a "budesonide composition" does not exclude solutions or suspensions where the budesonide is encapsulated in liposomes or biodegradable microspheres.

13. Plaintiffs' expert, Dr. Williams, states that the term "budesonide composition" excludes solutions or suspensions where the budesonide is encapsulated in liposomes or biodegradable microspheres because, in his opinion, the budesonide must be in direct contact with the solvent. I disagree.

14. Budesonide is a lipophilic steroid. A lipophilic or "lipid loving" molecule is one that dissolves in or is attracted to fats, oils or other lipids. Lipophilic molecules prefer to be in an environment where there is no water. Thus, because budesonide is lipophilic, it exhibits very low solubility in water. At a concentration that exceeds its solubility, budesonide will be present as a suspension—i.e., substantially undissolved—in water.

15. Figure 1 shows the chemical structure of a budesonide molecule.

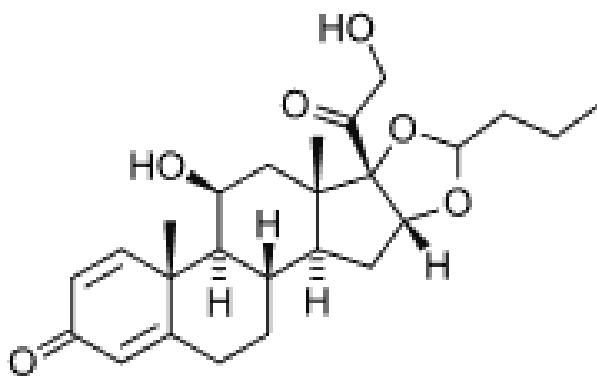


Figure 1: Budesonide

16. Because of its lipophilic properties, budesonide molecules will be attracted to other lipophilic molecules. Therefore, when added to water, budesonide particles might approach one another, and the strong association between the lipophilic particles would cause them to cohere, or stick together. Cohesion is not generally desirable in a suspension, particularly one intended to be used in a product for nebulization, such as Pulmicort Respules®,

since it effectively increases the particle size of the drug particles, potentially limiting the dose of drug delivered to the lungs.

17. Due to the tendency of budesonide particles to stick together, budesonide suspensions for nebulization will also typically contain a surfactant—surface active agent—or some other dispersant to prevent this from occurring. In fact, the ‘834 patent explicitly recognizes that surfactants may be added to the budesonide composition “to obtain an efficient dispersion of the glucocorticosteroid particles in the suspension.” (*See* Gross Decl. Ex. C at 5:24-26.)

18. The ‘603, ‘099 and ‘834 patents provide several examples of surfactants, such as polysorbates, that may be added to the claimed budesonide compositions to achieve dispersion of the budesonide particles. The ‘834 patent states that surfactants such as polyoxyethylene sorbitan fatty acid esters, preferably of the polysorbate or Tween™ groups” may be added to the suspension. (*See* Gross Decl. Ex. C at 5:24-46.) The ‘603 and ‘099 patents specifically state that budesonide may be delivered dispersed (i.e. suspended) in a solvent containing polysorbate. (*See* Gross Decl. Ex. A at 3:22-27; Gross Decl. Ex. B at 3:28-33.)

19. For Example, Figure 2 shows the chemical structure of polysorbate 80. Polysorbate 80 has a polyoxyethylene hydrophilic “head” portion, which has an affinity for aqueous substances, such as water. The hydrocarbon “tail” portion, on the other hand, has an affinity for lipophilic substances, such as budesonide.

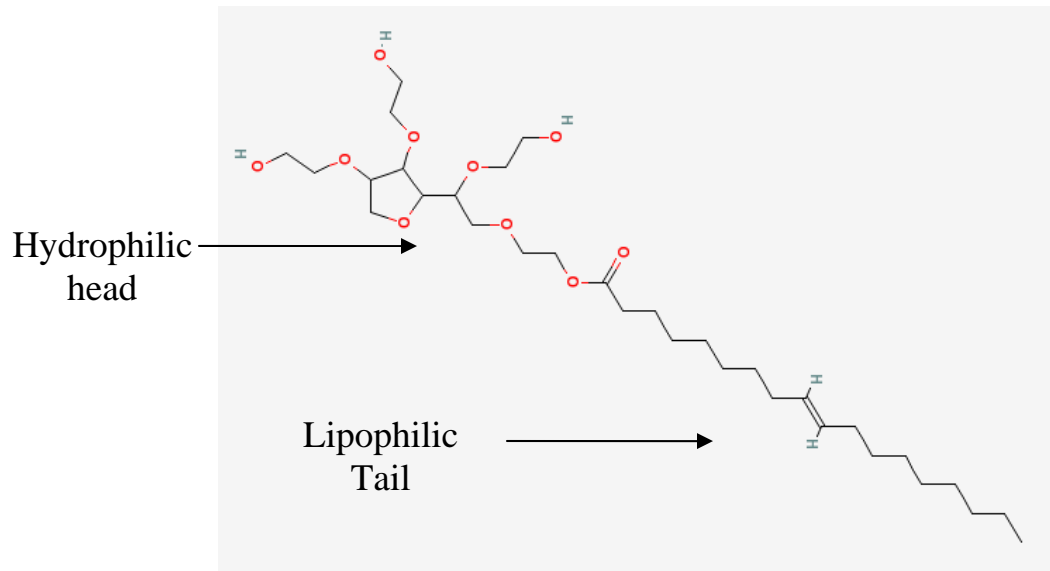


Figure 2: Polysorbate 80

20. It is likely, that when undissolved budesonide particles and polysorbate 80 are present together in an aqueous suspension, the polysorbate 80 will be present in the mixture at a higher concentration at the surface of budesonide particles than in the bulk aqueous matrix.

21. As shown in Figure 3, the “lipid loving” hydrocarbon tail of the polysorbate 80 will be oriented towards the lipophilic budesonide particles and the “water loving” hydrophilic head of the polysorbate 80 will be oriented towards the aqueous matrix. Surfactants such as polysorbate 80 enhance the physical stability of suspensions by preventing adjacent insoluble particles such as budesonide from approaching each other, because they partially cover the budesonide particle surface.

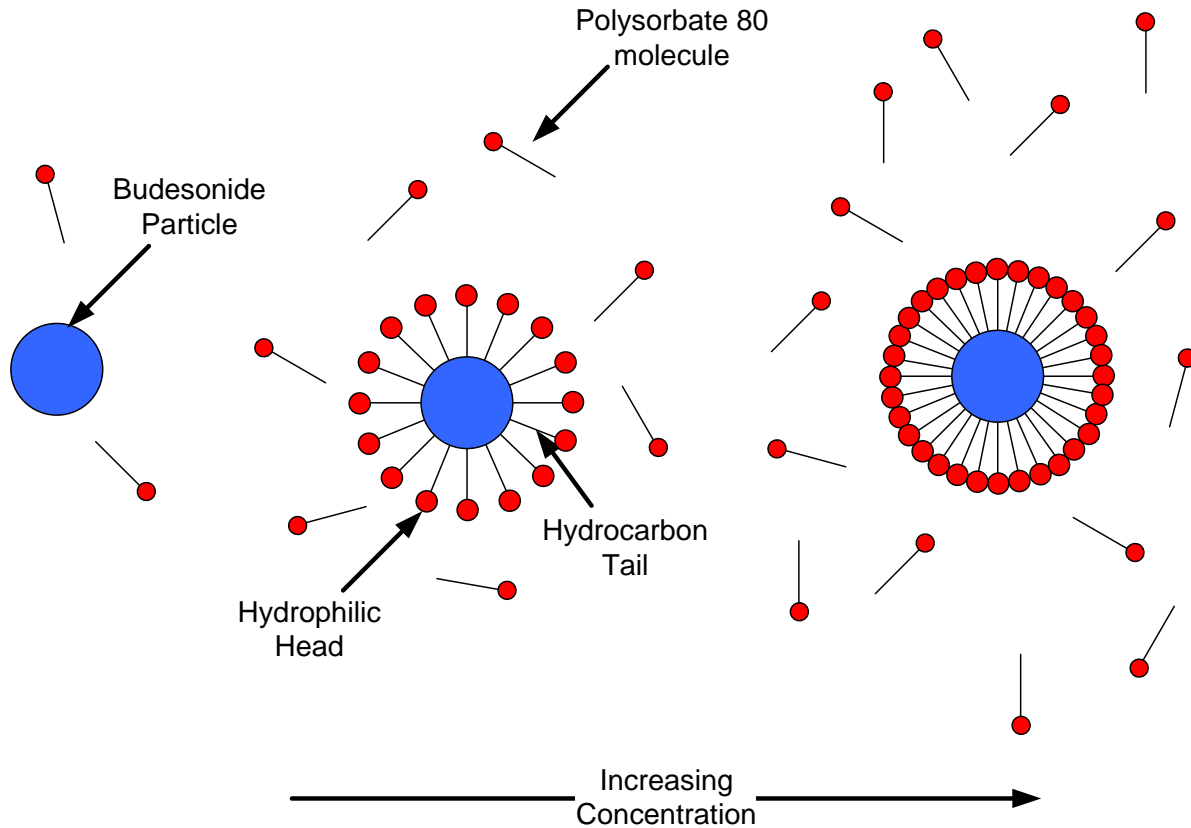


Figure 3: Interaction of polysorbate 80 with budesonide with increasing concentration of surfactant.

22. Generally, when a surfactant is added to a solvent (in this case, water or an aqueous matrix) at low concentration, it initially dissolves in the water as isolated molecules. If the concentration of surfactant is increased, it will preferentially occupy an interface. An interface is a phase change between liquid and gas (such as at the surface of liquid) or between liquid and a solid (such as where a budesonide particle meets the matrix in which it is dispersed).

23. If the concentration of surfactant is increased more, surfactant molecules may organize into molecular aggregates, such as micelles and liposomes. The concentration at which these molecular aggregates form is called the critical micelle concentration or CMC. In all cases, a proportion of the surfactant will be present as isolated molecules, a proportion will be present at the liquid surface and a proportion will be associated with budesonide particles.

24. A micelle is an aggregate of surfactant molecules dispersed in a liquid. A typical micelle in aqueous solution forms an aggregate with the hydrophilic “head” regions in contact with surrounding solvent, with the hydrophobic single tail regions oriented towards the micelle centre.

25. Liposomes are molecular aggregates primarily comprised of phospholipids. Phospholipids are a type of surfactant with two lipophilic (lipid loving) hydrocarbon tails and a hydrophilic (water loving) phosphate head.

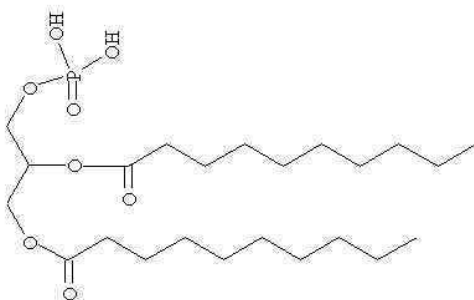


Figure 4: Typical Phospholipid

26. When dispersed in water, phospholipids can spontaneously form bilayer membranes, which are composed of two monolayer layer sheets of phospholipid molecules with their hydrophobic tails facing each other and their hydrophilic heads facing the aqueous medium. The membranes can enclose or entrap a portion of the aqueous phase. Equilibrium is established between free (isolated) phospholipid molecules and those which are self-associated to form a liposome.

27. Figure 5 shows a typical liposome, micelle and bilayer sheet or membrane.

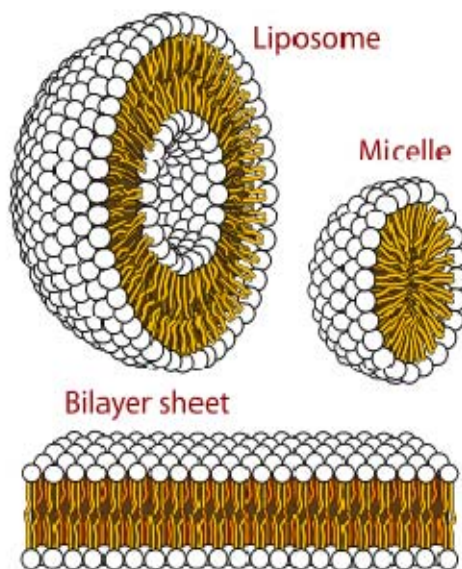


Figure 5: Structures that can be formed by phospholipids in aqueous solutions.

28. Liposomes are often used and studied in connection with drug delivery due to their unique properties. In fact, one main reason for using liposomes in a drug composition or formulation is to control the release of the drug.

29. The bonds between surfactant molecules and budesonide particles (due to adhesive forces) are relatively weak and there is a dynamic equilibrium between surfactant associated with the surface of budesonide particles and surfactant molecules that are associated with water molecules or with other surfactant molecules. Surfactant molecules will constantly be associating and disassociating with the budesonide particles in the suspension. Thus, at any instant of time, some budesonide molecules on the surface of a budesonide particles will be coated with surfactant molecules and some will be directly in contact with the bulk solution.

30. As stated above, all of the patents disclose that the budesonide may be provided in the budesonide composition with a polysorbate surfactant. Due to the dynamic equilibrium described above, even where a surfactant, such as polysorbate is added to the composition or

where the budesonide is encapsulated in liposomes or biodegradable microspheres, there will always be some budesonide molecules that are in direct contact with the solvent.

31. In addition, I disagree with Dr. Williams' statement that the encapsulation of budesonide in liposomes or biodegradable microspheres would prevent the "depot effect" from occurring.

32. In the pharmaceutical sciences, a "depot" is generally understood to mean a pool of drug that is released over time. Drug trapped inside a micelle or liposome can be regarded as a depot. Likewise, drug trapped inside muscle following an intra-muscular injection is sometimes referred to as a depot. Indeed, any drug slowly dissolving from a low solubility particle or a compact of particles covered with a layer of polymer or surfactant can be regarded as a depot. The term "depot" says nothing about the physical form of the drug which could be dissolved or present as a solid. Similarly, a "depot effect" can refer to anything resulting from the controlled or sustained release of a drug over time.

33. A "depot effect" would very likely occur in budesonide compositions containing a surfactant (such as polysorbate 80) or in compositions where the budesonide is encapsulated in liposomes or biodegradable microspheres. Budesonide could be trapped inside a liposome or micelle. It could also be present as particles covered with a layer of surfactant. In all cases a depot can be said to exist, although the rate at which drug is released from the depot will vary depending on the nature of the barrier surrounding the drug. When drug is released from a depot over time, the term "sustained release" is often used to describe the formulation or drug product.

34. One notable example of liposomes being used in a suspension for nebulization to control the release of an active ingredient in the lung is Arikace™.

35. The developmental drug product Arikace™, currently in Phase III clinical trials, comprises the antibiotic Amikacin encapsulated in liposomes. Arikace™ is indicated for the treatment of lung infections and, similar to Pulmicort Respules®, can be administered *once daily* via a nebulizer. Moreover, the literature for Arikace™ explains that the drug provides “sustained-release delivery” of the drug product to the lungs. One of ordinary skill in the art would understand this “sustained-release” to refer to a depot effect. (See “Arikace™ - A Potential New Weapon in the Treatment of Gram-Negative Lung Infections,” www.transaveinc.com/products.shtml#amik (last visited April 15, 2010) (attached hereto as Exhibit A); see also “Arikace™ - Liposomal Amikacin: Preclinical Summary,” www.transaveinc.com/fileSave%5CFINAL%20NACFC%20Poster%20slides10-17-2009.pdf (last visited April 15, 2010) (attached hereto as Exhibit B).

36. Those developing the Arikace™ product specifically reference the “sustained release” of the drug as allowing the drug to be effective when administered only once daily:

The sustained-release delivery of a drug may reduce dosing frequency to one time per day or less, thereby easing a patient's treatment burden and potentially improving patient compliance. Sustained release of the antibiotic above the therapeutic level (minimal level of drug needed to kill *Pseudomonas aeruginosa*) may also decrease the potential for the development of resistant strains of bacteria.

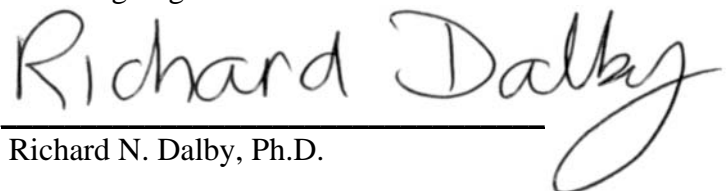
The overall product profile that Transave is working to develop for Arikace™ may potentially lead to broader patient usage in the U.S. and Europe and possibly result in: . . . (2) reduced dosing frequency, (3) decreased side effects, and; (4) decreased time for administration.

(Exhibit A).

I hereby declare under penalty of perjury that the foregoing is true and correct.

April 16, 2010

Date



Richard N. Dalby, Ph.D.